REMARKS

Applicants thank the Examiner for the review of the instant application. Claims 1-5 remain pending and are presented for further examination. For the reasons stated below, Applicants respectfully traverse the rejection of the pending claims.

Rejection Under 35 U.S.C. §101

The PTO maintains its rejection of Claims 1-5 under 35 U.S.C. § 101 as lacking a specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office Actions. The PTO asserts that one skilled in the art would not know how to use the claimed invention. According to the PTO, "the specification provides data showing an indeterminate increase in mRNA in one cancerous tissue.... However, there is no evidence regarding whether or not PRO1268 polypeptide levels are also increased ...." *Office Action* at 3. The PTO continues to rely on Pennica *et al.,* Haynes *et al.*, and Hu *et al.,* for the propositions that what is often seen is a lack of correlation between mRNA levels and increased peptide levels, that polypeptide levels cannot be accurately predicted from mRNA levels, and that the literature cautions researchers against drawing conclusions based on small changes in transcript expression levels. *Office Action* at 3. The PTO argues that further research is required to determine whether the PRO1268 polypeptide is differentially expressed, making the asserted utility not substantial.

Applicants incorporate by reference their previously submitted arguments, and for the reasons of record assert that the specification contains a disclosure of utility and therefore must be taken as sufficient to satisfy the utility requirement of 35 U.S.C. § 101. Applicants also submit that for reasons of record, the Examiner has not met the PTO's burden of providing evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility. However, even if the Examiner has met the PTO's initial burden, Applicants' rebuttal evidence previously submitted and additional evidence submitted herewith is sufficient to prove that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated previously, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

Applicants remind the PTO that the asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1268 polypeptide is expressed at least two-fold higher in kidney tumor tissue compared to normal kidney tissue;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, e.g. an increase, generally leads to a corresponding change in the level of the encoded protein, e.g. an increase;

3. Given Applicants' evidence that the mRNA for the PRO1268 polypeptide is differentially expressed in kidney tumor tissue compared to normal kidney tissue, it is more likely than not that the PRO1268 polypeptide is likewise differentially expressed in these tumors; the PRO1268 polypeptide and the claimed antibodies are therefore useful as diagnostic tools to distinguish kidney tumor tissue from normal kidney tissue.

Applicant's maintain that in light of all of the evidence, the PTO's arguments are not adequate to support the utility rejection of the claimed invention under 35 U.S.C. § 101.

The PTO has Concluded that the data in Example 18 are Sufficient to Establish the Utility of the Claimed Invention

As an initial matter, Applicants point out that in other applications filed by Applicants that rely on *data from the exact same disclosure, Example 18*, and in which the Applicants have submitted *substantially the same references* in support of their asserted utility, the PTO has concluded that: "[b]ased on the totality of evidence of record, **one of skill in the art would find it more likely than not that an increase in message as measured by RTPCR would be predictive of an increase in protein expression levels,** absent evidence to the contrary. Therefore, the data presented in Example 18, which demonstrates differential expression of nucleic acids encoding PRO1180, also supports a conclusion of differential expression of PRO1180 polypeptide. Therefore, one of ordinary skill in the art would be able to use the PRO1180 polypeptide diagnostically for distinguishing normal kidney and rectal tumor tissues compared to kidney tumor and normal rectal tissue, as asserted by Applicant." See *Examiners*

Reasons for Allowance in pending Application No. 10/063,529. See also *Examiners Reasons for Allowance* in Application No. 10/063,530, No. 10/063,524, No. 10/063,582, and No. 10/063,583, all of which conclude that the data presented in Example 18, which demonstrate differential expression of the nucleic acids encoding certain PRO polypeptides, also support a conclusion of differential expression of the PRO polypeptides, making the claimed PRO polypeptides and antibodies that bind the PRO polypeptides useful for diagnostic purposes.

Applicants therefore request that the Examiner recognize the utility of the claimed invention, supported by the data presented in Example 18 and the numerous cited references, as was done in the other applications referenced above.

The Previously Cited References Provide Evidence that Changes in mRNA Levels are Correlated with Changes in Protein Levels

Applicants turn to the PTO's argument that the evidence of differential expression of the gene encoding the PRO1268 polypeptide in kidney tumor tissue compared to normal kidney tissue is insufficient, in view of the teachings of Hu *et al.*

Applicants incorporate by reference their previously submitted arguments in regard to Hu *et al.* and will not reiterate those arguments here. However, Applicants will once again explain why the PTO's reliance on Hu is misplaced. Hu bases his conclusions on data generated from high throughput microarrays:

> In any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study. *Hu* at 405, left column, first paragraph (emphasis added).

As Applicants previously pointed out, Applicants are relying on a more accurate and reliable method of assessing changes in mRNA level, namely quantitative PCR analysis. Applicants submitted a reference by Kuo *et al.*, (Proteomics 5(4):894-906 (2005)), in which the authors state that PCR is a "more reliable and sensitive" than microarray technology. *Kuo et al.* at Abstract (emphasis added). Thus, even if accurate, Hu's statements regarding microarray studies are not relevant to the instant application which does not rely on microarray data.

Applicants maintain that Kuo supports their assertion that Applicants' PCR data are more accurate and reliable than the microarray data relied on by Hu. Because PCR is more accurate and reliable than microarrays, conclusions regarding the relevance of mRNA transcript changes

based on microarray data, such as those set forth in Hu, are not applicable to data generated using the more reliable method. Kuo supports this assertion because it is evidence that one of skill in the art would regard PCR as a more accurate and reliable method of assessing changes in mRNA.

Applicants next turn to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA for a particular protein, generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1268 polypeptide in kidney tumors, it is likely that the PRO1268 polypeptide is likewise differentially expressed in these tumors; and proteins differentially expressed in certain tumors, as well as the antibodies that bind such proteins, have utility as diagnostic tools.

The PTO's cited references are not contrary to Applicants' asserted utility

The PTO continues to rely on Pennica and Haynes, and newly cites Feroze-Merzoug as support for its argument that mRNA levels are not predictive of protein levels. Applicants have discussed at length in previous responses why Pennica and Haynes are not relevant to the issue of whether changes in mRNA level for a particular gene leads to changes in protein level. Applicants will not repeat their arguments here.

As for the teachings of Feroze-Merzoug relied on by the PTO, this reference is not referring to data generated in the subject report, but is instead referring to the observations of Gygi *et al.* (Mol. and Cell. Bio., (1999) 19(3):1720-30) and Waghray *et al.* (Proteomics, (2001) 1:1327-38). These references provide little or no evidence contrary to Applicants' assertions.

As Applicants have previously explained in regard to Haynes, Gygi attempted to discover a single numerical ratio common between all steady state mRNA levels and all steady state protein levels. Gygi's data showed that the steady state ratio of mRNA level:protein level varied for different genes, and hence no single numerical ratio existed. However, Applicants' assertions require no knowledge of a ratio between mRNA levels and protein levels, nor do Applicants' assertions require calculation of protein levels based on measured mRNA levels. Applicants simply assert that a change in mRNA level for a particular gene typically leads to a corresponding change in the encoded protein level. *See, e.g., First Grimaldi Declaration* at paragraph 7. Gygi was concerned with a different question, and, therefore, none of Gygi's data

or Feroze-Merzoug's conclusions based on Gygi's data, has any bearing on Applicants' assertions.

Regarding Feroze-Merzoug's reference to the report by Waghray *et al.*, Applicants emphasize that they make no assertion that differential protein levels always are accompanied by differential mRNA levels. The possibility that additional factors beyond differential mRNA levels also can lead to differential protein levels does nothing to undermine the assertion that differentially expressed mRNA typically leads to a corresponding differentially expressed encoded polypeptide. Waghray identified 44 proteins that were upregulated or downregulated in androgen-stimulated prostate cells. *Waghray* at 1333, right column. Of these 44 proteins, 29 were identified without ambiguity. *Id.* Of these 29 identified proteins, only 7 had a corresponding mRNA that changed by at least 2-fold as measured by the SAGE method. *Waghray* at 1336 (Table 4). Applicants' repeat that they make no assertion that differential protein levels must lead to similarly differential mRNA levels. Therefore, only these 7 instances that report differential mRNA levels bear relevance to Applicants' assertions.

Of these 7, five had values close to zero. Waghray teaches that when the value detected using SAGE "is close to zero, the quantitative nature of SAGE is compromised." *Waghray* at 1337, left column. Further, Waghray provides examples that when the differential SAGE levels were both close to zero, the levels measured by the more accurate PCR method showed only a small (<1.5-fold) difference. *Waghray* at 1337, left column, and Figure 1D. Thus in Waghray's study, only 2 discernably differentially expressed mRNAs also had measurements of the corresponding proteins.

Even these 2 instances may be artifacts of the mRNA and protein measurements made at different time points in Waghray's methods. The authors noted that the dynamic conditions of the experiments created fluctuating levels of both mRNA over time and that each of three transcripts displayed different dynamic behavior. *Waghray* at Fig. 1C and 1337. But Table 4 reports only 24 hour time points for each transcript, without providing a basis for selection of this arbitrary timepoint. None of the mRNA and protein data from Table 4, upon which the authors base their observation about the concordance of mRNA and protein levels, address the dynamic fluctuation taught by Waghray. Thus, Waghray teaches dynamic fluctuation of mRNA levels and the arbitrary timepoint selected to detect mRNA levels to be compared to protein levels,

regardless of degree of fluctuation of these levels. Further, Waghray provides no basis for presuming that the reported protein levels do not also exhibit the same variability due to the arbitrary 72 hour timepoint selected for measurement. More importantly, there is no basis in Waghray to consider that the 24 hour timepoint for mRNA levels is appropriate for comparing to the 72 hour timepoint for protein levels. Since both mRNA levels and protein levels can be expected to be in dynamic fluctuation, there is no basis in Waghray for concluding that the data in Table 4 should accurately reflect the relationship between mRNA and protein levels in the cell.

In sum, Waghray describes only 2 discernably differentially expressed mRNAs for which polypeptide levels were reported. However, based on Waghray's arbitrarily selected timepoints for measurement, there is no way to conclude that these 2 instances accurately reflect the relationship between mRNA and protein levels in the cell. As such, Waghray provides little or no basis to doubt Applicants' asserted utility. Thus, insofar as Feroze-Merzoug relies on Waghray for a teaching that changes in mRNA levels do not typically lead to similar changes in levels of the encoded polypeptide, this reliance is misplaced. Insofar as Feroze-Merzoug relies on Waghray for some other contention, such is not relevant to Applicants' asserted utility.

In conclusion, Applicants have previously shown that the Pennica and Haynes are simply not relevant to the issue of whether a change in mRNA levels leads to a corresponding change in the level of the encoded protein. Applicants have further shown that the publication by Feroze-Merzoug does not provide or refer to evidence that is contrary to Applicants assertions. As such, the PTO's arguments are not sufficient to satisfy the burden to "provide[] evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995).

Previously Submitted Exhibits 2-13 Are Relevant to the PTO's Argument Against Allowance of the Claims

Applicants continue to assert that it is well-established in the art that a change in the level of mRNA encoding a particular protein generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1268 polypeptide in kidney tumors, it is more likely than not that the PRO1268 polypeptide

is also differentially expressed; and proteins differentially expressed in certain tumors, and antibodies that bind such proteins, have utility as diagnostic tools.

Applicants previously submitted Exhibits 2-13, comprising 81 references, in support of their argument for the correlation between mRNA levels and protein levels. The PTO fails to address these references. Applicants maintain that the overwhelming evidence they have provided strongly supports Applicants' position.

The PTO discusses one reference, Wang, as a "comprehensive study," and makes no attempt to assert that this reference, or any other reference submitted by Applicants, does not demonstrate that changes in mRNA levels typically lead to corresponding changes in the encoded polypeptide. Instead, the PTO argues that, based on Applicants' data in Example 18, "[i]t cannot be determined what the function of the protein is in those tissues" and "Applicants do not know the function of the PRO1268 polypeptide. For this reason, detecting the PRO1268 mRNA or polypeptide by means of the claimed antibody has no specific [utility], since it is not useful to detect a protein for which a function has not yet been identified." *Office Action* at 8.

Applicants submit that a lack of known function for PRO1268 in cancer does not prevent its use as a diagnostic tool for cancer - one does not need to know why PRO1268 is differentially expressed, or what the consequences of the differential expression are, in order to exploit the differential expression to distinguish tumor from normal tissue.

In fact, the Revised Interim Utility Guidelines promulgated by the PTO recognize that proteins which are differentially expressed in cancer have utility. The caveat in Example 12 states that the utility requirement is satisfied where a protein is expressed on melanoma cells but not on normal skin, and that antibodies against the protein can be used to diagnose cancer. The position of the PTO requiring a known role for PRO1268 in cancer for utility is also inconsistent with the analogous standard for therapeutic utility of a compound where "the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an 'immediate benefit to the public' and thus satisfies the utility requirement." M.P.E.P. §2701.01 (emphasis in original). Here, the mere identification of altered expression in tumors is relevant to diagnosis of tumors, and, therefore, provides an immediate benefit to the public.

Accordingly, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO1268

mRNA is differentially expressed in kidney tumor tissue compared to normal kidney tissue, the PRO1268 polypeptide will also be differentially expressed in kidney tumor tissue compared to normal kidney tissue. This differential expression of PRO1268 and related polypeptides make the claimed antibodies useful as diagnostic tools for cancer, and requirement of a specific function to establish utility is contrary to PTO policy. Further, it is well recognized that a diagnostic utility of a claimed compound is sufficient to fulfill the requirements of 35 U.S.C. §101.

In addition to the publications submitted by Applicants in support of their asserted utility, Applicants have previously submitted the Polakis Declaration in support of their position that in general, changes in mRNA levels correlate with changes in protein levels. Applicants submit herewith as Exhibit 1 a second Declaration by Dr. Polakis (Polakis II) that presents evidentiary data in Exhibit B. Exhibit B of the Declaration identifies 28 gene transcripts out of 31 gene transcripts (i.e., greater than 90%) that showed good correlation between tumor mRNA and tumor protein levels. As Dr. Polakis' Declaration (Polakis II) says "[a]s such, in the cases where we have been able to quantitatively measure both (i) mRNA and (ii) protein levels in both (i) tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA." Accordingly, Dr. Polakis has provided the facts to enable the Examiner to draw independent conclusions.

Applicants also submit herewith a copy of a declaration by Randy Scott, Ph.D. (attached as Exhibit 2). Dr. Scott is an independent expert in the field of molecular diagnostics, with over 15 years experience. He is the author of over 40 scientific publications in the fields of protein biology, gene discovery, and cancer, and is inventor on several issued patents. His curriculum vitae is attached to the declaration. In paragraph 10 of his declaration, Dr. Scott states:

> One reason for the success and wide-spread use of the DNA microarray technique, which has led to the emergence of a new industry, is that generally there is a good correlation between mRNA levels determined by microarray analysis and expression levels of the translated protein. Although there are some exceptions on an individual gene basis, it has been a consensus in the scientific community that elevated mRNA levels are good predictors of increased abundance of the corresponding translated proteins in a particular tissue. Therefore, diagnostic markers and drug candidates can be readily and efficiently screened and identified

using this technique, without the need to directly measure individual protein expression levels. *Scott Declaration* at ¶10 (emphasis added).

Applicants submit the opinion of yet another expert in the field that changes in mRNA level for a particular protein in a given tissue generally lead to a corresponding change in the level of the encoded protein. Importantly, Dr. Scott also states that, contrary to the contentions of the PTO, diagnostic markers can be identified "without the need to directly measure individual protein expression levels." This opinion is supported by Dr. Scott's extensive experience in the field, as well as the fact that an entire industry has developed around technology used to assess differential mRNA expression. As stated previously, there would be little reason to study changes in mRNA expression levels if those changes did not result in corresponding changes in the encoded protein levels.

The case law has clearly established that in considering affidavit evidence, the PTO must consider all of the evidence of record anew. *In re Rinehart,* 531 F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976) and *In re Piasecki,* 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985). "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument." *In re Alton,* 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir. 1996)(quoting *In re Oetiker,* 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992)). Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner." *Id.* at 1583. Applicants also respectfully draw the PTO's attention to the Utility Examination Guidelines which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." Part IIB, 66 Fed. Reg. 1098 (2001).

In summary, Applicants have submitted herewith two additional expert Declarations in addition to the declarations and over 115 references already of record, which support Applicants' asserted utility, either directly or indirectly. This evidence overwhelmingly supports the assertion that in general, a change in mRNA expression level for a particular gene leads to a corresponding change in the level of expression of the encoded protein. As Applicants have previously

acknowledged, the correlation between changes in mRNA level and protein level is not exact, and there are exceptions. However, Applicants remind the PTO that the asserted utility does not have to be established to a statistical certainty, or beyond a reasonable doubt. *See M.P.E.P.* at § 2107.02, part VII (2004). Therefore, the fact that there are exceptions to the correlation between changes in mRNA and changes in protein does not provide a proper basis for rejecting Applicants' asserted utility. Applicants submit that considering the evidence as a whole, with the overwhelming majority of the evidence supporting Applicants' asserted utility, a person of skill in the art would conclude that Applicants' asserted utility is "more likely than not true." *Id.*

The PTO's Position is Inconsistent with the Utility Guidelines and the Courts

In response to Applicants' evidence and arguments, the PTO takes the position that Applicants must present specific evidence directly demonstrating the utility of the claimed antibodies – specifically, direct evidence of differential expression of PRO1268 polypeptide in tumor and normal tissue. Applicants submit that this requirement is inconsistent with the Utility Guidelines and the courts.

Adopting the PTO's standard for utility would result in a per se rule that a difference in mRNA expression cannot establish a utility for the encoded polypeptide and antibodies thereto. Thus, the PTO chooses to heighten the utility requirement to require specific, direct evidence of utility when there are exceptions to a generally accepted rule that is relied upon for utility. This heightened utility requirement is inconsistent with the Utility Guidelines and the courts. There is no requirement that utility be dispositively proven:

> Furthermore, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." *In re Irons,* 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965) ... Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. *M.P.E.P.* 2107.02 VII (emphasis in original).

There is no requirement that only direct evidence of utility is sufficient to establish utility. Instead, it is established that indirect evidence that is reasonably indicative of utility is sufficient to fulfill the requirements of 35 U.S.C. §101. *Nelson v. Bowler*, 626 F.2d 853, 856. Furthermore, there is no requirement that indirect evidence necessarily and always prove actual

utility. Instead, there only need be a reasonable correlation between the indirect evidence and the asserted utility. *Id.* at 857, *Cross v. Iizuka*, 753 F.2d 1040, 1050-1051. The indirect evidence need not absolutely prove the asserted utility. All that is required is that the tests be reasonably indicative of the asserted utility. In other words, there need only be a sufficient correlation between the indirect evidence and the utility so as to convince those skilled in the art, to a reasonable probability, that the novel compound will possess the asserted utility. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564.

In the present case, Applicants submit that their evidence (differential mRNA expression) is reasonably linked to the asserted utility (diagnostic use of the encoded polypeptide and specific antibodies). Insofar as it is uncontested that differential mRNA expression is reasonably linked to differential polypeptide expression, Applicants submit that such linkage is sufficient to fulfill the requirements of 35 U.S.C. §101 as provided by the guidance of the Utility Guidelines and the courts.

In conclusion, the PTO's heightened requirement for establishing utility of the presently claimed antibodies is contrary to the Utility Guidelines and the courts: it is sufficient to present evidence of differential mRNA expression since it is understood in the art that differential mRNA expression is reasonably linked to differential polypeptide expression. As discussed above, even if the PTO has presented evidence that changes in mRNA expression is not <u>always</u> correlated with changes in protein expression, Applicants' overwhelming rebuttal evidence is more than sufficient to establish that changes in mRNA level typically lead to corresponding changes in protein level. As such, Applicants have established that it is more likely than not that one of skill in the art would believe that because the PRO1268 mRNA is differentially expressed in kidney tumors as compared to normal kidney tissue, the PRO1268 polypeptide will likewise be differentially expressed in these tumors. Accordingly, when the evidence is applied to the proper standard for utility, it is clear that this differential expression of the PRO1268 polypeptide establishes the utility of the polypeptide and antibodies that bind the polypeptide as diagnostic tools for cancer, particularly kidney tumor. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Conclusion

The PTO has asserted that the state of the art is such that polypeptide levels cannot be accurately predicted from mRNA levels. Applicants have addressed each of the PTO's supporting references and shown that they are either irrelevant, or taken as a whole, actually support Applicants' assertion that a change in mRNA level leads to a corresponding change in the level of the encoded protein. In addition, Applicants have submitted expert declarations, textbook excerpts, and over 115 scientific publications which support Applicants' asserted utility.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed antibodies as diagnostic tools. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing **some** beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely... A commercially successful product is not required... Nor is it essential that the invention accomplish all its intended functions... or operate under all conditions... partial success being sufficient to demonstrate patentable utility... In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed antibodies to the PRO1268 polypeptide set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO maintains its rejection of Claims 1-5 as lacking enablement. The PTO states that because the claimed invention is not supported by either a specific and substantial asserted

utility or a well established utility, one skilled in the art would not know how to use the claimed invention.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed antibodies. Applicants respectfully request that to the extent the enablement rejection is based on a lack of utility, the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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